Form PTO-1390

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
BONN-063

U.S. APPLICATION NO.
09/936078

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/00577	March 9, 2000	March 9, 1999

TITLE OF INVENTION:
METHOD AND APPARATUS FOR FLUID TRANSFER BY SEVERAL CENTRIFUGING OPERATIONS

DATE:
September 7, 2001

APPLICANT(S) FOR DO/EO/US
Bruno COLIN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [XX] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. [XX] This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [XX] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [XX] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [XX] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [XX] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [XX] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [XX] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [XX] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [XX] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [XX] Other items or information:

    a. WO 00/53317 (first page only)
    b. International Search Report (PCT/ISA/210)
    c. Written Opinion (PCT/IPEA/408)
    d. International Preliminary Examination Report (PCT/IPEA/409)

U.S. Application No. 09/936078	International Application No. PCT/FR00/00577	Attorney's Docket No BONN-063

17. [XX] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO. **$860.00**	860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482). . **$690.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$710.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . . **$ 1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). . . . . **$ 100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	7 - 20	0	x $ 18.00	$	
Indep.claims	2 - 3	0	x $ 80.00	$	
Multiple dependent claim(s) (if applicable)			+ $270.00	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 860.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
			SUB TOTAL =	$ 860.00	
Processing fee $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	$ 860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$ 860.00	
				Amount to be: refunded	$
				charged	$

a. [XX] A Credit Card Payment Form in the amount of $ 860.00 to cover the above fee is attached.

b. [ ] Please charge my Deposit Account No. 50-1258 in the amount of $_____ to cover the above fees. Two copies of this sheet are enclosed.

c. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1258 . Two copies of this sheet are enclosed.

NOTE: **Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to review (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

James C. Lydon
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314

James C. Lydon
Signature

James C. Lydon
Name

30,082
Registration Number

September 7, 2001
Date

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Bruno COLIN

Serial Number: New Patent Application

Filed: September 7, 2001

For: METHOD AND APPARATUS FOR FLUID TRANSFER BY SEVERAL CENTRIFUGING OPERATIONS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

September 7, 2001

Please amend this application, prior to calculation of the filing fee, as follows:

IN THE SPECIFICATION:

Page 1, between the title and the first heading, please insert the following:

This application is a U.S. National Stage of International application PCT/FR00/00577, filed March 9, 2000 and published on September 14, 2000 in the French Language.

IN THE CLAIMS:

Please cancel claims 1-8 without prejudice or disclaimer.

Please add new claims 9-15 as follows:

9. (New) A method for transferring a fluid from at least one initial compartment to at least one receiving compartment, via at

least one transfer channel, the transfer being driven by centrifugal force, comprising:

performing a first centrifugation operation to transfer a fluid from an initial compartment towards an intermediate compartment via a primary transfer channel, and

performing at least one secondary centrifugation operation where the axis of centrifugation is different from that of the first centrifugation operation, to transfer said fluid from said intermediate compartment towards a receiving compartment via a secondary transfer channel,

wherein said intermediate compartment is associated with at least two receiving compartments, each receiving compartment being linked to the intermediate compartment via a secondary transfer channel, and

wherein it consists in performing at least one secondary centrifugation operation to drive and distribute the fluid present in said intermediate compartment towards at least two receiving compartments.

10. (New) An apparatus for transferring a fluid, comprising

a body which contains at least one initial compartment,

at least one receiving compartment,

at least one transfer channel,

at least two centrifugation axes,

one primary axis to drive the fluid from the initial compartment towards an intermediate compartment via a primary transfer channel, and

at least one secondary axis, which is different from the primary axis, to transfer said fluid from the intermediate compartment towards the receiving compartment via a secondary transfer channel,

wherein each centrifugation axis cuts substantially perpendicularly an imaginary axis which passes through both the compartment containing the fluid and the compartment to which the fluid is to be transferred by centrifugation around the axis concerned, and positioned between said compartment containing the fluid and the edge of said apparatus;

said intermediate compartment is associated with at least two adjacent receiving compartments, each receiving compartment being linked to the intermediate compartment by means of a secondary transfer channel, and these receiving compartments are connected to only one centrifugation axis that enables a distribution between the receiving compartments to be obtained.

11. (New) The apparatus of claim 10, wherein each transfer channel linking a pair of compartments is positioned substantially along an

imaginary axis passing through both compartments at either end of the channel concerned.

12. (New) The apparatus of claim 10, wherein each transfer channel linking a pair of compartments is connected to one centrifugation axis.

13. (New) The apparatus of claim 10, wherein each transfer channel is straight and passes through the center of gravity of the two compartments located at either end of said transfer channel.

14. (New) The apparatus of claim 10, wherein each transfer channel contains a means of closure such as a bead valve which can block the passage of the fluid which has either already been transferred or which is to be transferred.

15. (New) The apparatus of claim 10, wherein a configuration of the intermediate compartment at the points of intersection with the secondary transfer channels leading to the adjacent receiving compartments is such that, under the action of the centrifugal force, the fluid in said intermediate compartment is directed to and equally distributed into said adjacent receiving compartments.

New National Stage Application
PRELIMINARY AMENDMENT

PATENT

IN THE ABSTRACT:

Please replace the original abstract with the attached Substitute Abstract.

REMARKS

This Preliminary Amendment cancels claims 1 - 8, adds new claims 9 - 15, amends the specification and presents a new Abstract. The amendment to the specification inserts a reference to parent application PCT/FR00/00577 pursuant to 37 C.F.R. § 1.78. New claims 9-15 are based on the amended claims presented during International Preliminary Examination, and have been further amended by eliminating multiple dependencies and drawing reference numerals, and by otherwise conforming the claims to U.S. practice. The Substitute Abstract is based on the PCT Abstract. A version with markings to show changes made is attached as an Appendix. Claims 9-15 are pending.

An Information Disclosure Statement is attached.

It is not believed that any fee is required for entry and consideration of this Preliminary Amendment. Nevertheless, the Commissioner is authorized to charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Prompt and favorable examination of the application are earnestly requested.

Respectfully submitted,

James C. Lydon
Reg. No. 30,082

Atty. Case No.: BONN-063
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

Enclosures:
Appendix
Abstract of the Disclosure
Information Disclosure Statement

New National Stage Application
PRELIMINARY AMENDMENT

PATENT

APPENDIX

Version With Markings to Show Changes Made

IN THE SPECIFICATION:

The paragraph inserted between the title and the first heading on page 1 is new.

IN THE CLAIMS:

Claims 1-8 have been canceled.

Claims 9-15 are new.

IN THE ABSTRACT:

The Substitute Abstract is new.

ABSTRACT OF THE DISCLOSURE:

A method and apparatus for transferring a fluid (2) from at least one initial compartment (4) towards a final receiving compartment (6) via at least one transfer flow path (9 and 10), the transfer being carried out by the action of a centrifugal force, the method including: performing a first, primary centrifugation operation for transferring the fluid (2) from its initial compartment (4) towards an intermediate compartment (5), via a primary transfer flow path (9), and performing at least one secondary centrifugation operation, where the axis of centrifugation (8) is different from that (7) of the first centrifuging operation, to transfer the fluid (2) from the intermediate compartment (5) towards the final receiving compartment (6) via a secondary transfer flow path (10). The method and apparatus are particularly applicable to microfluidic devices used in biology.

Method and Apparatus for Fluid Transfer by Several Centrifuging Operations

DESCRIPTION

The invention concerns a method for transferring a fluid – especially a liquid – from an initial compartment towards a receiving compartment via a transfer channel, the transfer being carried out by way of a centrifugal force.

The background art is given in document FR-A-2.678.379 which pertains to the transfer of a liquid into a device meant for sampling and delivering a preset volume of liquid. This device is tubular in shape and contains around its edge a blind spiral channel whose axis of symmetry is the axis of centrifugation. When the device is placed with the opening of its internal channel in contact with a liquid, the liquid enters the device when it is spun in one direction, and leaves it when it is spun in the other direction.

This device can only be used for sampling and distributing the sampled liquid. The displacement of the liquid inside the device cannot be directed. The versatility of this system is very limited, all the more so since centrifugation needs to be continued for as long as the liquid is required to stay inside the device.

According to another embodiment, centrifugation can be more versatile and therefore incorporated into an apparatus in which multiple biological reactions can be allowed to take place. There

are numerous documents which have much in common, e.g. patents US-A-3,744,975, US-A-4,123,173 and US-A-4,225,558, which propose a flat, cylindrical apparatus in which the center is occupied by a rotation axis. This axis therefore makes it possible to transfer liquids contained in the apparatus from the center of said apparatus towards its periphery by the action of the centrifugal force.

However, driving transfer in the opposite direction, i.e. using a centripetal force, is not possible. Therefore, the liquids can only be displaced using centrifugal force.

Documents US-A-4,812,294, EP-A-0.297.394 and US-A-4,788,154 describe devices and methods which make it possible to drive liquids in different directions under the action of the centrifugal forces resulting from the use of different centrifugation axes.

Nevertheless, none of these documents deals with any particular configuration that associates the axis through which the centrifugal force is applied and, on the one hand, the arrangement of, first, the initial or intermediate compartment or, secondly, the intermediate or receiving compartment, and on the other hand, the transfer channel between these compartments. Moreover, the applicant's invention makes it possible to distribute liquids in predetermined proportions according to the configuration and the presence of at least two intermediate compartments per initial

compartment and/or at least two receiving compartments per intermediate compartment.

In accordance with this invention, a method with a more versatile implementation is proposed. This method makes it possible to obtain movements in all the device's compartments without the effects of a one-step centrifugation, and to distribute liquids in established proportions.

The invention also concerns a method for the implementation of such an apparatus.

To this effect, this invention concerns a method for transferring a fluid from at least one initial compartment towards at least one receiving compartment via at least one transfer channel, the transfer being driven by centrifugal force. The method consists in:

- performing a first centrifugation operation, said to be primary, to transfer the fluid from the initial compartment to an intermediate compartment via a primary transfer channel, and
- performing at least a second centrifugation operation, said to be secondary, whereof the axis of centrifugation is different from that of the first centrifugation operation, to transfer the fluid from the intermediate compartment towards the receiving compartment via a secondary transfer channel,

and it is characterized in that the intermediate compartment is associated with at least two receiving compartments, each receiving compartment being joined to the intermediate compartment via a secondary transfer channel, and in that it consists in performing at least one secondary centrifugation operation to drive the fluid present in said intermediate compartment towards at least two receiving compartments.

The invention also concerns a fluid transfer apparatus consisting of a body which contains at least one initial compartment, at least one receiving compartment and at least one transfer channel. This apparatus also has at least two centrifugation axes, a primary axis to transfer the fluid from the initial compartment towards an intermediate compartment via a primary transfer channel, and at least one secondary axis – different from the primary axis – to transfer said fluid from the intermediate compartment to a receiving compartment via a secondary transfer channel. This apparatus is characterized in that each centrifugation axis crosses substantially at right angle an imaginary axis passing through both the compartment containing the fluid and the compartment where the centrifugal force (resulting from centrifugation around the axis concerned) is to drive the fluid, and positioned between said compartment containing the fluid and the edge of said apparatus.

According to an alternative embodiment, each transfer channel linking a pair of compartments is positioned substantially along the imaginary axis passing through both compartments at either end of the channel concerned.

According to another alternative embodiment, each transfer channel linking a pair of compartments is associated with a centrifugation axis.

According to a further alternative embodiment, each transfer channel is straight and passes through the center of gravity of the two compartments located either side of the transfer channel concerned.

According to yet another alternative embodiment, each transfer channel is fitted with a means of closure such as a bead valve which blocks the passage of the fluid which has either already been transferred or which is to be transferred.

According to another alternative embodiment, the intermediate compartment is associated with at least two adjacent receiving compartments, each receiving compartment being linked with the intermediate compartment through a secondary transfer channel. These receiving channels are associated with a single centrifugation axis which makes it possible to distribute the fluid to the two adjacent receiving compartments.

According to another alternative embodiment, the configuration of the intermediate compartment at the points of intersection with the secondary transfer channels leading to adjacent receiving compartments is such that, under the action of the centrifugal force, the fluid is directed towards said channels and is equally distributed between said adjacent receiving compartments.

Such an apparatus can be used for the analysis of one or more different liquid samples to identify one or more analytes, using any method, be it a simple or complex method and be it based on one or more different reagents, depending on the chemical, physical or biological nature of the analyte being tested. The technical principles defined hereafter are not restricted to any single, specific analyte; the only required condition being that the analyte must either be dissolved or in suspension in the test sample. In particular, the test process being used can be performed on a homogenous, heterogeneous or mixed form.

One particular, non restricted mode of such a device, concerns biological tests for the detection and/or quantitative determination of one or more ligands, in which the assay involves one or more anti-ligands. The word ligand is taken to mean any biological species, e.g. an antigen, a fragment of an antigen, a hapten, a nucleic acid, a fragment of nucleic acid, a hormone or a vitamin. One example of an application of the test methods

concerns immunoassays, whatever their particulars and whether the assay is direct or based on competition. Another example of an application concerns the detection and/or quantitative determination of nucleic acids, including all operations required for such detection and/or quantitation from any sample containing the target nucleic acid species. Among such diverse operations, the following could be specified: lysis, melting, concentration, enzyme-mediated nucleic acid amplification, and detection modalities which include a hybridization step using, for example, a DNA chip or a labeled probe. Patent application WO-A-97/02357 stipulates the various stages involved in the case of nucleic acid analysis.

The accompanying drawings are given by way of example and are not to be taken as in any way limiting. They are intended to make the invention easier to understand.

Figure 1 represents an overhead view of a first embodiment of this invention, before the first centrifugation operation.

Figure 2 represents an overhead view of a first embodiment of this invention, after the first and before the second centrifugation operation.

Figure 3 represents an overhead view of a first embodiment of this invention, after the second centrifugation operation.

Figure 4 represents an overhead view of a second embodiment of this invention.

Finally, Figure 5 represents an overhead view of a third embodiment of this invention.

This invention concerns a new method for transferring a liquid (2) in a transfer apparatus (1) consisting of a body (3). As can be seen in the Figures, the apparatus (1) is substantially in the form of a parallelepiped although only the upper side of the apparatus or card (1) is in view.

In terms of production, the card is manufactured by the machining of special plastic material, e.g. impact polystyrene (reference: R540E from the Goodfellow company) which is compatible with the liquids being processed. For industrial-scale production, the card could be manufactured by precision molding, but any other manufacturing method (including those used in the semi-conductor industry as stipulated in patent application WO-A-97/02357) may be used for the manufacturing of said card.

A first embodiment is represented in Figures 1 to 3. The purpose of the method is to transfer a sample (2) from an initial compartment (4) to four receiving compartments (6). Thus, the apparatus (1) contains one primary initial compartment (4) seen on the left of all these Figures. It is possible to pass via an intermediate compartment (5) which is substantially "kidney-

shaped"; this intermediate compartment (5) being located in a median position in terms of the overall channel, between the initial compartment (4) and the receiving compartments (6) (of which there are four in these Figures). However, the receiving compartments are not found on the far right in these figures, that position being occupied by the intermediate compartment (5). Details on the spatial configuration of the different compartments will be given later in the context of the different steps in the transfer process.

Of course, there are channels to mediate transfer from one compartment to another. The first is a primary transfer channel (9) which joins the initial compartment (4) to the intermediate compartment (5); other channels, i.e. secondary transfer channels (10) join the intermediate compartment (5) with the receiving compartments (6).

In the embodiment represented in Figures 1 to 3, each receiving compartment (6) has its own secondary transfer channel (10) so there is an independent channel/compartment (6/10) pair for each receiving compartment (6).

It can be seen that the overall configuration of the compartments is such that the initial compartment (4) is located on the left, the intermediate compartment (5) is located on the right, and the receiving compartments (6) are located between the initial

and intermediate compartments (4 and 5). Therefore, full transfer is only possible if a multiple centrifugation operation is performed. This is fully explained in Figures 1 to 3.

Thus, in Figure 1, the liquid sample (2) is only present in the initial compartment (4). In this position, the liquid sample (2) is in fact in its initial position, either because it has been introduced directly into this compartment (4) or because it has been introduced into this compartment (4) via an independent transfer channel. No such transfer channel is represented in these Figures.

Referring to Figure 2, a first centrifugation operation is performed in direction C1 around the primary centrifugation axis (7). In this case, the liquid (2) is driven in the direction of arrow F1 towards the intermediate compartment (5) via a primary transfer channel (9). As is clearly shown in this Figure, the liquid (2) is driven as far as it can go from axis 7, i.e. into intermediate compartment (5).

Referring to Figure 3, a second centrifugation operation is performed in direction C2 around a secondary centrifugation axis (8). When the apparatus is spun in direction C2, it can be seen that the liquid (2) will be driven into the receiving compartments (6) via the secondary transfer channels (10). This displacement occurs in the direction of arrow F2 in Figure 3. Again, the liquid

samples (2) distributed in receiving compartments (6) will be driven as far as they can go from the centrifugation axis (8).

So that the liquid sample (2) does not return towards initial compartment (4) from the intermediate compartment (5), the latter has a very special shape near the exit point of the secondary transfer channels (10). Thus, as mentioned above, the intermediate compartment (5) is substantially "kidney-shaped" in that one side of said intermediate compartment (5) consists of two lobes. These lobes are located on either side of the point where the primary transfer channel (9) crosses the intermediate compartment (5). Each lobe is associated with two channels (10) so the shape of compartment (5) means that the liquid is directed and driven towards the receiving compartments (6) during the second centrifugation operation, thereby preventing, or at least minimizing the return of liquid via channel (9). Of course, a valve (not shown in the Figure) could be installed on channel (9) in order to block any return of liquid, if necessary. In order to minimize the amount of liquid returning into the primary transfer channel (9), the volume of liquid contained in the lower lobe of the intermediate compartment (5) must be greater than the volume of liquid to be displaced into the two compartments (6) located below channel (9) in Figures 1 to 3. The volume of the lobe of compartment 5 is well defined, on one side by a half-line

perpendicular to channel 9 and located at the end of this channel (9), and on the other side by the intersection between the secondary channels (10) and this same compartment (5). The same applies to the upper lobe. Preferably, in order to avoid the possibility of fluid communication between the two compartments (6), the volume of the lobe ought also to be less than the total volume of the compartments (6) and the two channels (10) associated with said compartments taken together. In one embodiment, both lobes have the same volume. In another embodiment, each of the two lobes has a different volume. In one embodiment, the receiving compartments have exactly the same volume. The shape and dimensions of the channels (10) are chosen by those skilled in the art to insure even distribution of the liquid between the various receiving compartments. In another embodiment, the receiving compartments have different volumes.

The total volume of liquid which can be transferred by this device can vary from 0.5 to 5000 microliters (advantageously between 2 and 2000 microliters and preferably between 5 and 1000 microliters). The volume of the initial compartment covers the same range or may be substantially greater than the total transferred volume.

By way of example, in the embodiment represented in Figures 1 to 3, the volume of the initial compartment (4) is between 0.1 and

0.5 ml for transfer of 100 microliters of liquid to the intermediate compartment (5), the volume of which is more or less equivalent to that of compartment 4. The second centrifugation operation in direction C2 sends 25 microliters into each receiving compartment (6) with a precision of below 5%.

Of course, the shapes mentioned as well as the number of channels and compartments are in no way limiting and other configurations of the card (1) are entirely possible, as are different numbers of compartments or channels. This is represented, for example, in Figure 4 in which the card is substantially square-shaped in top view.

In this case, there is an initial compartment (14) in the center of the body (13), this compartment being linked to four intermediate compartments (15) via four primary transfer channels (19). In order to simplify centrifugation operations and make it easier to distribute the liquids in the desired way, the four intermediate compartments are arranged symmetrically with respect to one another.

It can be seen that, as before, there is one primary centrifugation axis (17) and a secondary centrifugation axis (18), but in addition, there are two extra centrifugation axes (12). The positions of all these axes are precisely defined. Thus, if one takes the center point of the initial compartment (14) and traces

a half-line from this point to the center of gravity of each of the intermediate compartments (15), each centrifugation axis (17, 18, or 12) is found on this half-line at a point between the intermediate compartment (15) and the edge of the card or transfer apparatus (11).

Similarly, there are receiving compartments (16) which are linked to the intermediate compartment (15) via secondary transfer channels (20). It is immediately clear that these secondary transfer channels (20) have a point of intersection with the intermediate compartment (15), through which one can draw a straight line that passes through the center of gravity of the intermediate compartment (15). This straight line is actually substantially perpendicular to the half-line between the center of gravity of the initial compartment (14) and the center of gravity of the intermediate compartment (15). Now, it is easy to see that, with a liquid sample in the center, i.e. in the initial compartment (14), it is possible to choose which intermediate compartment into which to transfer all or part of the liquid (2) (not shown on Figure 4). Thus, if the apparatus 11 is spun around centrifugation axis 17, the liquid (2) will be driven towards the intermediate compartment (15) located on the left of Figure 4. Once the liquid (2) has reached this position, it will be possible to spin around centrifugation axis (18) in order to transfer said liquid (2) out

of the intermediate compartment (15) into the receiving compartment (16) at the top. If, on the other hand, it is desired to send the liquid to the lower receiving compartment (16), the card will have to be spun around centrifugation axis (12) at the top. It is also entirely possible that the liquid (2) has to be returned back to the initial compartment (14), or perhaps to the intermediate compartment (15) located on the right. In this case, centrifugation will have to be performed around axis (12) located on the left of the Figure. Therefore, it is easy to appreciate the versatility of such a system and the great number of different directions in which the liquid can be sent within the same card.

Figure 5 represents a third and final embodiment of the apparatus (21). It is substantially identical to that depicted in Figure 4, but it can be seen that there is an extra centrifugation option once the liquid has arrived in one of the receiving compartments (26). Thus, each receiving compartment (26) is associated with two terminal transfer channels (32) which lead to two terminal compartments (31). In order to drive a liquid (2) into a terminal compartment (31) (shown in Figure 5), it will be necessary to introduce the sample into the initial compartment (24) located at the center point of the body (23) of the apparatus (21), then to spin the apparatus around (27) in order to drive the sample (2) into the intermediate compartment (25) located on the left of

the Figure, next to perform a centrifugation around 28 in order to transfer said sample from the intermediate compartment (25) into the receiving compartment (26), and finally to continue the centrifugation operation around 28 in order to drive the liquid (2) into the terminal compartment (31).

Of course, in order to obtain tighter control over the movement of the liquids (2) which can be introduced, it would be possible to introduce means for blocking their passage. Capillary action could be exploited with these channels but it would also be possible to introduce valves into the channels which could be used to either open or close them. Such valves are thoroughly described in Patent Application FR98/11383 submitted by the applicant on September 9 1998 and entitled "A device in which reactions can be performed, a transfer system between devices and a method for using such a system."

Similarly, although not shown in Figures 1 through 4, the apparatus described in this invention includes inlets and/or outlets to insure that it works properly.

In order to be effective, centrifugation does not have to be performed at a very high speed. A force of between 2 and 10 g (g is the symbol for the acceleration due to the force of gravity), and preferably of between 3 and 5 g, is perfectly adequate for non-

viscous biological fluids. For more viscous fluids, forces of between 10 and 200 g could be used.

In order to make centrifugation operations as effective as possible, it is possible to have as many centrifugation axes as there are transfer channels joining pairs of adjacent compartments between which liquids are to be transferred. Thus, in Figures 4 and 5, there are just four centrifugation axes (27, 28 and 22). It would also be possible to imagine including centrifugation axes at the corners of each device (11 or 21) in order to make it easier to transfer the liquid to receiving compartments (16 or 26) or into the terminal compartments (31). Moreover, and yet again to improve the efficacy of centrifugation operations, these channels are preferably straight.

REFERENCES

1. A transfer apparatus according to a first embodiment
2. Fluid or liquid
3. Body
4. Initial compartment
5. Intermediate compartment
6. Receiving compartment
7. Primary centrifugation axis
8. Secondary centrifugation axis
9. Primary transfer channel
10. Secondary transfer channel
11. A transfer apparatus according to a second embodiment
12. Other centrifugation axes
13. Body
14. Initial compartment
15. Intermediate compartment
16. Receiving compartment
17. Primary centrifugation axis
18. Secondary centrifugation axis
19. Primary transfer channel
20. Secondary transfer channel
21. A transfer apparatus
22. Other centrifugation axes

23. Body

24. Initial compartment

25. Intermediate compartment

26. Receiving compartment

27. Primary centrifugation axis

28. Secondary centrifugation axis

29. Primary transfer channel

30. Secondary transfer channel

31. Terminal compartment

32. Terminal transfer channel

C1. Direction in which the apparatus (1) is spun for the first centrifugation operation

C2. Direction in which the apparatus (1) is spun for the second centrifugation operation

F1. Displacement of the liquid (2) as a result of the first centrifugation operation

F2. Direction of flow of the liquid (2) as a result of the second centrifugation operation

CLAIMS

1. A method for transferring a fluid (2) from at least one initial compartment (4, 14 or 24) to at least one receiving compartment (6, 16 or 26), via at least one transfer channel (9 and 10, 19 and 20, or 29 and 30), the transfer being driven by centrifugal force. The method consists in:

- performing a first centrifugation operation (C1), said to be primary, to transfer the fluid (2) from an initial compartment (4, 14 or 24) towards an intermediate compartment (5, 15 or 25), via a primary transfer channel (9, 19 or 29), and

- performing at least one more centrifugation operation, said to be secondary, whereof the axis of centrifugation (8) is different from that of the first centrifugation operation (7), to transfer the fluid (2) from an intermediate compartment (5, 15 or 25) towards a receiving compartment (6, 16 or 26) via a secondary transfer channel (10, 20 or 30),

characterized in that the intermediate compartment (5, 15 or 25) is associated with at least two receiving compartments (6, 16 or 26), each receiving compartment (6, 16 or 26) being linked to the intermediate compartment (5, 15 or 25) via a secondary transfer channel (10, 20 or 30), and in that it consists in performing at least one secondary centrifugation operation (C2) to drive the

fluid present in said intermediate compartment (5, 15 or 25) towards at least two receiving compartments (6, 16 or 26).

2. An apparatus (1, 11 or 21) for transferring a fluid (2), consisting of a body (3, 13 or 23) which contains at least one initial compartment (4, 14 or 24), at least one receiving compartment (6, 16 or 26) and at least one transfer channel (9, 19 or 29 or alternatively 10, 20 or 30). This apparatus also has at least two centrifugation axes (7 and 8, 17 and 18, or 27 and 28), one primary axis (7, 17 or 27) to drive the fluid (2) from the initial compartment (4, 14 or 24) towards an intermediate compartment (5, 15 or 25) via a primary transfer channel (9, 19 or 29), and at least one secondary axis (8, 18 or 28), which is different from the primary axis (7, 17 or 27), to transfer said fluid (2) from the intermediate compartment (5, 15 or 25) towards the receiving compartment (6, 16 or 26) via a secondary transfer channel (10, 20 or 30),

characterized in that each centrifugation axis (7 or 8, 17 or 18, or 27 or 28) cuts substantially perpendicularly an imaginary axis which passes through both the compartment containing the fluid and the compartment to which the fluid is to be transferred by centrifugation around the axis concerned, and positioned between

said compartment containing the fluid and the edge of said apparatus (1, 11 or 21).

3. The apparatus according to claim 2, characterized in that each transfer channel (9 or 10, 19 or 20, or 29 or 30) linking a pair of compartments is positioned substantially along the imaginary axis passing through both compartments at either end of the channel concerned (9 or 10, 19 or 20, or 29 or 30).

4. The apparatus according to either of claims 2 or 3, characterized in that each transfer channel (9 or 10, 19 or 20, or 29 or 30) linking a pair of compartments (4, 14 or 24 or 6, 16 or 26, and 5, 15 or 25) is associated with one centrifugation axis (7 or 8, 17 or 18, or 27 or 28).

5. The apparatus according to any of claims 2 through 4, characterized in that each transfer channel (9 or 10, 19 or 20, or 29 or 30) is straight and passes through the center of gravity of the two compartments (4, 14 or 24 or 6, 16 or 26, and 5, 15 or 25) located at either end of said transfer channel (9 or 10, 19 or 20, or 29 or 30).

6. The apparatus according to any of claims 2 through 5, characterized in that each transfer channel contains a means of closure such as a bead valve which can block the passage of the fluid which has either already been transferred or which is to be transferred.

7. The apparatus according to any of claims 2 through 6, characterized in that the intermediate compartment (5, 15 or 25) is associated with at least two adjacent receiving compartments (6, 16 or 26), each receiving compartment (6, 16 or 26) being linked to the intermediate compartment (5, 15 or 25) via a secondary transfer channel (10 20 or 30), and in that these receiving compartments (6, 16 or 26) are associated with a single centrifugation axis (8, 18 or 28) which makes it possible to distribute the liquid to the adjacent receiving compartments (6, 16 or 26).

8. The apparatus according to claim 7, characterized in that the configuration of the intermediate compartment (5, 15 or 25) at the points of intersection with the secondary transfer channels (10, 20 or 30) leading to the adjacent receiving compartments (6, 16 or 26) is such that, under the action of the centrifugal force (C1 or C2), the fluid (2) is directed to said channels in such a way that it is

equally distributed to said adjacent receiving compartments (6, 16 or 26).

ABSTRACT

"A method and apparatus for fluid transfer by successive centrifugation operations"

BIOMERIEUX S.A.

The present invention concerns a method for transferring a fluid (2) from at least one initial compartment (4) to at least one receiving compartment (6), via at least one transfer channel (9 and 10), the transfer being carried out by the action of a centrifugal force, the method consisting in:

- performing a first centrifugation operation (C1), said to be primary, for transferring the fluid (2) from an initial compartment (4) to an intermediate compartment (5), via a primary transfer channel (9), and
- performing at least one second centrifugation operation, said to be secondary, whereof the axis of centrifugation (8) is different from that (7) of the first centrifugation operation, to transfer the fluid (2) from the intermediate compartment (5) towards the receiving compartment (6) via a secondary transfer channel (10).

The invention also concerns an apparatus (1) for the implementation of such a method.

The invention is characterized in that the intermediate compartment (5) is associated with at least two receiving compartments (6), each receiving compartment (6) being linked to the intermediate compartment (5) via a secondary transfer channel (10), and in that it consists in performing at least one secondary centrifugation operation to redirect the fluid contained in said intermediate compartment (5) towards at least two receiving compartments (6).

The invention is particularly applicable for the micromanipulation of fluids in biological applications.

Figure 1

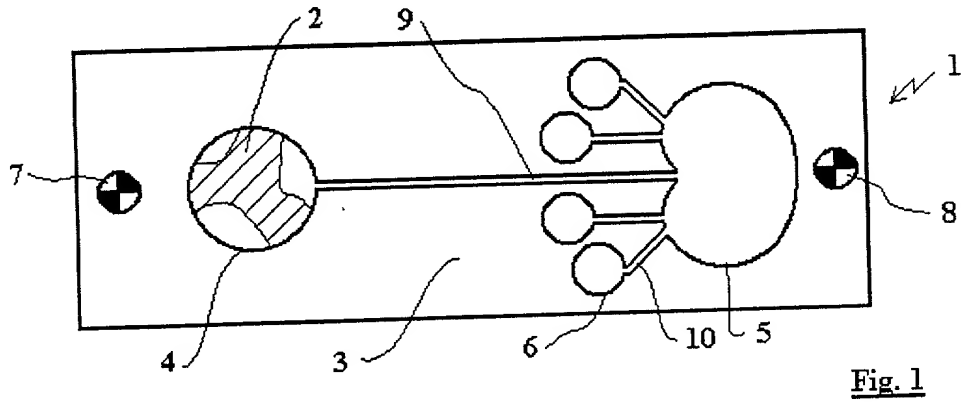

Fig. 1

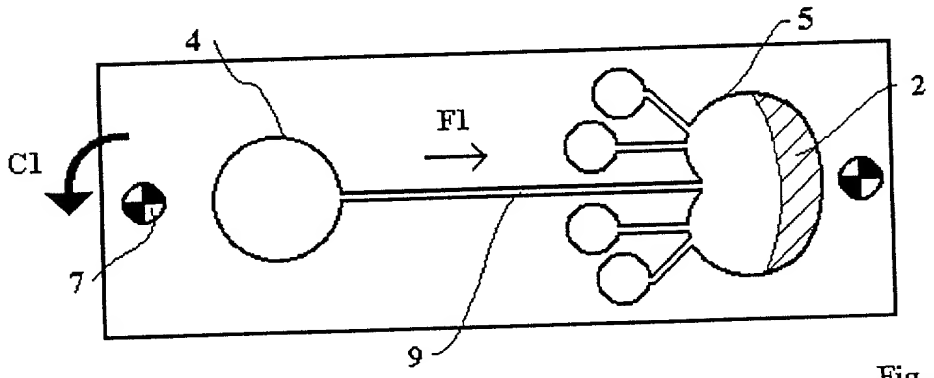

Fig. 2

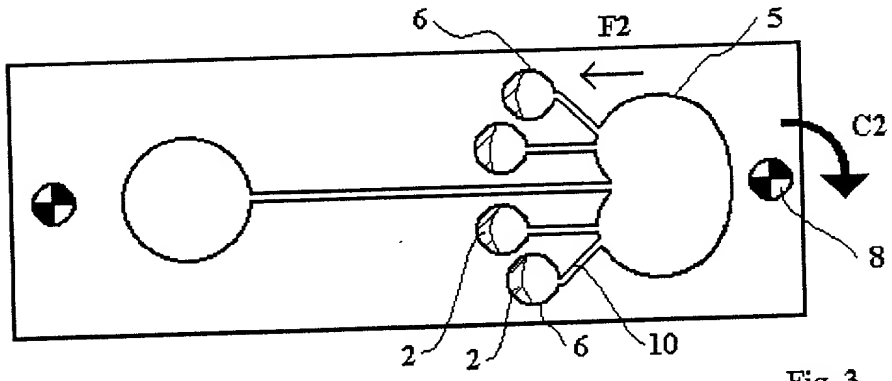

Fig. 3

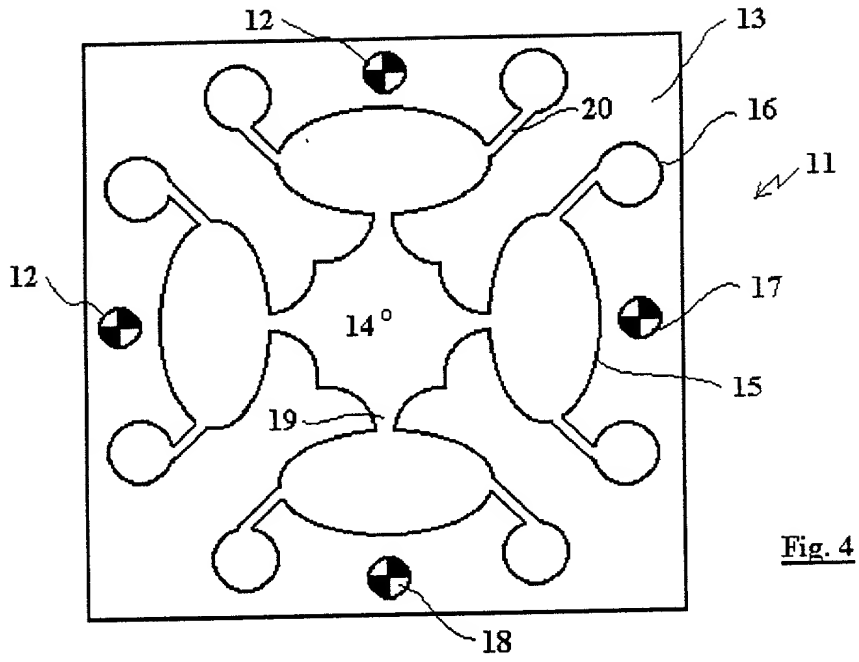

Fig. 4

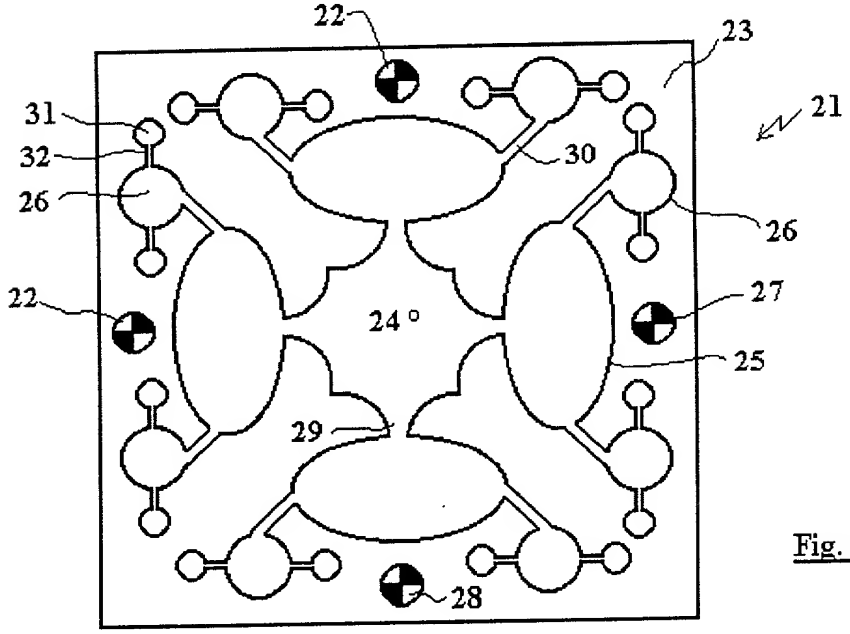

Fig. 5

Docket No. BONN-063

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled (INSERT TITLE) Method and apparatus for fluid transfer by several centrifuging operations

the specification of which

(Check one of 1, 2, or 3.)

1. __ is attached hereto.
2. XX was filed on March , 9, 2000 as International PCT Application Serial No.PCT/FR00/00577 and was amended on March 13, 2001 (if applicable).
3. __ was filed on _____ as U.S. Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application for which priority is claimed:

(List prior foreign applications.)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
	99/03032	FRANCE	March 9, 1999	X Yes ___ No
				___ Yes ___ No

___ See attached list for additional prior foreign applications

I hereby claim the benefit under Title 35, United States Code, §120, of any United States application listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status)
(Application Serial No.)	(Filing Date)	(Status)

I hereby appoint as principal attorney James C. Lydon, Reg. No. 30,082.

Please direct all communications to the following address:

James C. Lydon
100 Daingerfield Road
Suite 100
Alexandria, VA 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first or sole inventor: Bruno COLIN
Inventor's Signature: Bruno Colin BC Date: 31 August 2001
Residence: : 23, Chemin des Garennes - F-69280 Marcy l'Etoile - France
Citizenship: French
Post Office Address: same as above FRX

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